REVIEW MEMORANDUM

Date: August 8, 2001
From: Jennifer L. Goode, Biomedical Engineer, ODE/DCRD/PVDB (HFZ-450)
To: **P010022**
Subject: Cohesion Technologies' CoSeal Surgical Sealant

This review memo contains information about:

Attached to this review memo are:

IDE Submission History

This PMA is related to an IDE sponsored by Cohesion Technologies, Inc. In the IDE clinical study, CoSeal was used to seal PTFE graft anasotomoses in peripheral arterial and venous reconstructions (including arterial bypass and patch grafts and AV shunts). This study has been completed, and is being used to support this PMA.

PMA Submission History

April 12, 2001	PMA filed.
May 25, 2001	**PMA Filing Letter** – informed sponsor of decision to bring device to panel.
June 15, 2001	/A1 – response to Office of Compliance request for additional GMP/QSR information
July 20, 2001	100 Day teleconference with the sponsor – addressed 11 deficiencies identified in the review to that point (deficiencies were emailed and faxed to sponsor 7/19/01). During the teleconference, the sponsor asked a few clarifying questions, and then discussed the timeframes for submission of responses.
August 3, 2001	**100-Day Status Letter** (faxed and mailed to the sponsor) - included 11 deficiencies addressed in the 100 Day meeting and one additional deficiency that was emailed to the sponsor in draft on 8/1/01.

Also included in the review of this submission are a series of faxed submissions from the sponsor between May 3, 2001 and July 9, 2001, in response to interactive requests from the agency during the review period. This information will be formally submitted to the PMA when the sponsor submits their next official amendment to the file (in response to the 8/3/01 100-Day Status Letter).

Review Team

The following CDRH personnel contributed to the review of this PMA:

Jennifer Goode (ODE/DCRD)	Team Leader/Lead Reviewer, and Biocompatibility, Sterilization, and Engineering Reviewer
Elisa Harvey, Ph.D., DVM (ODE/DCRD)	Chief, Peripheral Vascular Devices Branch
Paul Chandeysson, M.D. (ODE/DCRD)	Clinical Reviewer
Susan Zhou, Ph.D. (OSB/DBS)	Statistical Reviewer
Srilekha Das, Ph.D. (OST/DMMS)	Chemistry Reviewer
Charles Durfor, Ph.D. (ODE/DGRND)	Chemist (assisted with chemistry and biocompatibility review)
Rosalie Elespuru, Ph.D. (OST/DLS)	Genotoxicologist (assisted with biocompatibility review)
Hector Herrera, M.D. (ODE/DRARD)	Urologist (assisted with biocompatibility review)
Lisa Kennell (ODE/DCRD)	Biologist (assisted with sterilization review)
John Langone, Ph.D. (OST/DLS)	Immunologist (assisted with biocompatibility review)
Katharine Merrit, Ph.D. (OST/DLS)	Biologist (assisted with biocompatibility review)
Rao Nimmagada, Ph.D. (ODE/DRARD)	Chemist (assisted with chemistry and biocompatibility review)
Ruth Weiss	Patient Labeling Reviewer
Mary Ann Fitzgerald (OC/DOE3)	Manufacturing/Quality Systems Reviewer
Liliane Brown (OC/DBM)	Bioresearch Monitoring Reviewer

Device Description

CoSeal Surgical Sealant is a hydrogel that is formed when two synthetic derivatized polyethylene glycol (PEG) polymers are mixed together and applied to tissue. The hydrogel acts as a sealant by adhering to itself and to the tissues it contacts. The PEG polymers are supplied separately as powders in syringes. The powder syringes are connected to a second set of syringes containing their corresponding reconstitution buffers. CoSeal is prepared by syringe-to-syringe mixing of the buffers with their corresponding powders resulting in two syringes, each containing a dissolved PEG. Component A is made by mixing powdered pentaerythritol polyethylene glycol ether tetra-succinimidyl glutarate (also identified as COH102 PEG or SAN058 in the body of the PMA document) and a [redacted] buffer (also identified as SAN 054 in the body of the PMA document) with a [redacted]. Component B is made by mixing powdered pentaerythritol polyethylene glycol ether tetra-thiol (also identified as COH206 PEG or SAN059 in the body of the PMA document) and a [redacted] buffer (also identified as SAN055 in the body of the PMA document) with a [redacted]. The dissolved PEGs are then co-extruded during administration to the tissue site using a delivery system. This Standard Delivery System is composed of a syringe support, a syringe clip, and various types of applicator tips. The hydrogel is designed to form within seconds after application and resorb over several weeks.

Principle of Operation

When the two PEG's that make up CoSeal are mixed together, [redacted]. The hydrogel is formed by the [redacted].

Reactions between multiple arms of the PEGs result in a covalently bonded three-dimensional matrix. The PEG end-groups can also chemically react with the tissue matrix to form covalent bonds, thereby providing a firm bond between the final CoSeal hydrogel and the surrounding tissue.

Conversely, the CoSeal hydrogel creates a mechanical bond with PTFE and Dacron graft materials. Covalent bonds cannot occur because of the non-reactive surfaces designed into these materials. However, when CoSeal is first applied, it is able to partially penetrate the nooks and crannies of the irregular graft surfaces. Within seconds of application the CoSeal partially penetrates the natural holes found in the graft and CoSeal begins to set, thereby effectively molding itself to the graft.

Degradation occurs in situ because the resulting CoSeal hydrogel contains [redacted].

Packaging

- PEG-Buffer Syringes: radiation stable, foil pouch consisting of laminated polyester
- Delivery System: radiation stable, nylon peel pouch consisting of laminated polyester with polyethylene sealant layer

The packaging systems were designed to meet the requirements of two standards (ISO 11607 – Packaging for terminally sterilized medical devices; and ISO 11137 – Sterilization of health care products: Requirements for validation and routine control – Radiation Sterilization) and have been tested to meet packaging specifications for seal strength and burst pressure. FDA reviewed this data, and has no outstanding questions.

Sterilization

This product is sterilized by Electron Beam Radiation ( ) to a Sterility Assurance Level (SAL) of 10^{-6}. The sponsor's radiation sterilization protocol was validated to meet the requirements of the following standards:

- ISO 11137 – Sterilization of health care products: Requirements for validation and routine control – Radiation Sterilization;
- EN 552 – Sterilization of medical devices: Validation and routine control of sterilization by irradiation; and
- EN 556 – Sterilization of medical devices: Requirements for terminally sterilized devices to be labeled "Sterile"

Validation data was provided in this PMA application, and FDA has no outstanding questions.

Pre-Clinical Bench Testing

The sponsor conducted a series of bench tests to demonstrate the functional properties of the CoSeal hydrogel as follows:

- SET TIME: Forms a polymerized hydrogel within seconds of application to a moist surface
- GEL STRENGTH & ADHERENCE: Seals a 27 gauge defect in PTFE pressurized graft (at)
- DELIVERY SYSTEM PERFORMANCE: Mixes two components of gel without clogging delivery system, and without leaks from luer lock connections. Applied gel subjected to burst testing with acceptable results.
- DEGRADATION STUDY: Degrades into monomers and tetramers by day .

FDA has asked the sponsor for some minor clarifications regarding the functional testing (8/3/01 100 Day Letter).

Shelf Life Testing

The sponsor is requesting a Shelf Life of 18 months, and has conducted a series of stability tests to support this request. The sponsor provided 9 month (on 3 production lots) and 12 month (on one pre-production lot) real-time data for product stored at 2-8°C (the storage temperature of the product). This data demonstrates that the product remains within specification. The sponsor also provided data from stability testing at elevated temperatures that they believe supports an extension of the shelf life out to 18 months. FDA has asked the sponsor for some minor clarifications regarding the stability testing at elevated temperatures (8/3/01 100 Day Letter) to determine whether the data supports the extended shelf life.

Transit Testing

The sponsor conducted a series of tests to demonstrate that after summer and winter temperature cycling conditions, the packaging was not damaged, and the packaged buffers and powders continued to meet the product's chemical specifications. The product was then polymerized and the polymerized CoSeal hydrogel continued to meet the product's functional specifications.

Biocompatibility Testing

Biocompatibility studies on the final CoSeal formulation were conducted in accordance with ISO 10993. Studies revealed that the hydrogel is:

- NON-CYTOTOXIC: in agar overlay, direct contact, and MEM elution studies;
- NOT A GENOTOXIN: non-mutagenic, and non-clastogenic using PBS elutions; and non-clastogenic in an in vivo mouse micronucleus assay (Note that FDA has asked the sponsor for some minor clarifications regarding the test protocol);
- NON-TOXIC: studied acutely and long-term in [redacted] day implantation studies in various surgical sites in rats, rabbits, dogs, sheep and cow models
  - NOTE 1: product is fully degraded by Day [redacted] (not detectable macroscopically or histologically by day [redacted])
  - NOTE 2: potential for renal toxicity resulting from PEG degradation was addressed in a [redacted] day dosing study in rats, and no renal toxicity was seen for CoSeal volumes an order of magnitude larger than those used clinically.
  - NOTE 3: in a canine iliac model no adverse hemocompatibility results were seen. (Note that FDA has asked the sponsor for some minor clarifications regarding the hemocompatibility of this product).

For implant materials in contact with cardiovascular tissue for a duration of contact between 24 hours and 30 days, ISO 10993 also recommends that material-mediated pyrogenicity testing be considered.

Neither material-mediated nor LAL (bioburden-mediated) pyrogenicity testing was provided in the original PMA application. **Because of the increased numbers of fevers seen in the CoSeal group of the US study (see clinical section below), FDA is concerned that the product itself (materials and/or bioburden from the manufacturing process) has not yet been ruled out as a potential source for pyrogens.**

Panel Please Note:

There will be a panel question on the implications of the clinical findings regarding elevated temperature for the assessment of device safety. (Please also see the discussion regarding the clinical findings on page 6 of this memorandum.)

FDA concerns with the lack of pyrogenicity testing were relayed to the sponsor (faxed 7/19/01), and at the 100 Day meeting on 7/20/01, the sponsor indicated that this testing had been initiated and results would be submitted to the agency once the studies were completed. **The sponsor has included pre-clinical pyrogenicity testing information in Part 5.a.iv.2 (Summary of Pyrogen Data) of this panel package. Prior to the panel mailing, FDA did not have the opportunity to review this information.**

The sponsor also conducted a guinea pig sensitization test using CoSeal, and determined that the product is "non-sensitizing." FDA does not agree that the data submitted supports this conclusion.

Panel Please Note:

There will be a panel question regarding whether additional pre-clinical testing, clinical follow-up, or clinical post market studies are necessary to evaluate the sensitization potential of this material in humans, or if it is sufficient to warn physicians and users that this material has been shown to cause an allergic response in an animal model, and its effect on humans is unknown.

The actual sensitization test report is included in Part 6.d. (Covance Final Report) of this panel package, and is summarized below:

Dermal Sensitization Test
TEST ARTICLES: CoSeal ([redacted][1][2] CoSeal buffer
POSITIVE CONTROL: 0.1%DNCB in 80% EtOH
ANIMAL MODEL: 18 male albino Guinea Pigs
Group 1: 6/CoSeal sensitized
Group 2: 6/non-sensitized irritation control
Group 3: 6/DNCB sensitized
GRPS 1 & 3 – INDUCTION PHASE 1: @ 1day (0.3ml subcutaneous injections of CoSeal and DNCB respectively)
GRPS 1 & 3 – INDUCTION PHASE 2: @ 15 days (0.3ml subcutaneous injections of CoSeal and DNCB respectively)
GRP 1 CHALLENGE PHASE: @ 29 days (0.1 ml intradermal injections of [redacted], and buffer)
GRP 2 CHALLENGE PHASE: @ 29 days (0.1 ml intradermal injections of [redacted], DNCB and buffer)
GRP 3 CHALLENGE PHASE: @ 29 days (0.1 ml intradermal injection of DNCB)
OBSERVATION: @ 24,48&72hrs after last intradermal injection for dermal reactions (erythema & edema and wheal dimensions), and daily for clinical observations
NON-PRIMARY IRRITANTS – all animals untreated during induction (GRP 2), exhibited no dermal reactions at the sites treated with [redacted] & PBS during challenge (DNCB site elicited mild to moderate erythema, mean wheal size of 73.3 mm^2 on day 30; reaction intensity decrease on days 31 & 32)
SENSITIZATION RESULTS:
GRP 1 – [redacted] exhibited mild to moderate erythema (mean wheal size [redacted] mm^2 on day 30), reaction intensity decreased on days 31 & 32; [redacted] & PBS exhibited no dermal reactions
GRP 3 – DNCB exhibited moderate to severe erythema (mean wheal size 196.2 mm^2 on day 30), reaction intensity decrease on days 31 & 32

Assessment: While [redacted] exhibited mild to moderate erythema in the sensitized group, this sensitization response was significant only at 24 hrs. (when compared to the non-sensitized group). Histology showed mild to moderate local inflammation in both the sensitized and non-sensitized animals, but both groups were negative for IgG.

Buffer controls showed no measurable sensitization response, histolgy showed mild inflammation in both sensitized and non-sensitized animals (some focal ulceration, fibrosis, and calcification), but both groups were negative for IgG.

DNCB sensitized animals had significantly stronger response to DNCB challenge than non-sensitized controls with 3 of 6 sites with focal skin ulcerations. In 2 of the 6 non-sensitized animals, 1 had a necrotic sebaceous gland and one had a scab. Histology showed moderate to marked inflammation in both sensitized and non-sensitized animals, and inflammation in the sensitized animals included eosinophils (associated with hypersensitivity reactions). 2 of the 6 sensitized animals stained positive for IgG.

Summary Results: Mild to Moderate Sensitization Response seen in CoSeal group at 24 hours post challenge, resolved by 48 hour time point

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[redacted][1].

John Langone, Ph.D., an Immunotoxicologist in the Office of Science and Technology, Division of Life Sciences, was consulted regarding this sensitization data. Based on this consultation, the sponsor was asked to address the following deficiency (faxed to sponsor 7/19/01). **The sponsor has included portions of their response to this deficiency in Part 6.a. (Pre-clinical Sensitization Study – Executive Summary) of this panel package. Prior to the panel mailing, FDA did not have the opportunity to review this information.**

> *In your report on guinea pig sensitization testing (PMA page 02 043), you state that while [redacted] (PEG hydrogel) exhibited mild to moderate erythema in the sensitized group, this sensitization response was significant only at 24 hours (when compared to the non-sensitized group). Histology showed mild to moderate local inflammation in both the sensitized and non-sensitized animals, but both groups were negative for IgG. In your summary information (PMA page 01 038), you state that "no significant sensitization effects occurred with CoSeal."*
>
> *FDA believes that when testing for a cell-mediated delayed type hypersensitivity (DTH) reaction (Type IV), a significant response at 24 hours is considered a positive response in DTH testing, and indicates that CoSeal may also be a human sensitizer. Therefore, please provide the following additional information regarding the sensitization testing you conducted.*

a. Provide a justification for the test procedure used (species, numbers of animals per group, subcutaneous instead of intra or epidermal applications, etc.);

b. Summarize the test results according to an accepted severity index [e.g., ASTM F 720 (1996) Standard Practice for Testing Guinea Pigs for Contact Allergens: Guinea Pig Maximization Test]; and

c. Explain why you tested for IgG and how the results from this testing address the sensitization potential of CoSeal™.

US Pivotal Clinical Study

An IDE randomized clinical trial of CoSeal was done in 153 patients who were referred for implantation of ePTFE vascular grafts for arterial bypass or for vascular access. Almost all of the patients (n=148) had some bleeding at the suture lines, and were therefore randomized to be treated either with CoSeal (n=74) as the test surgical sealant or Gelfoam and thrombin (n=74) as the control surgical sealant. There was no statistically significant difference in the number of sites achieving hemostastis within 10 minutes of treatment when comparing CoSeal to the control treatment. The time to achieve sealing was generally less in the patients treated with CoSeal, although there was no statistically significant difference in the transfusion requirements.

Effectiveness Results: Hemostasis w/in 10 minutes (Primary Endpoint)

	CoSeal	Control	p-value
Number of sites treated	136	128	
Success by site (all indications)	117/136 (86%)	108/128 (84%)	0.763
Bypass Grafts	40/53 (76%)	34/45 (76%)	0.958
AV Grafts	76/80 (95%)	71/79 (90%)	0.196
Patch Grafts	1/3 (33%)	3/4 (75%)	0.478
Brisk Bleeding	29/39 (74%)	25/34 (74%)	0.583
Oozing	88/97 (91%)	83/94 (88%)	0.467

Effectiveness Results: Immediate Hemostasis (Secondary Endpoint)

	CoSeal	Control	p-value
Number of sites treated	136	128	
Success by site (all indications)	64/136 (47%)	25/128 (25%)	<0.001
Bypass Grafts	22/53 (42%)	5/45 (11%)	<0.001
AV Grafts	42/80 (52%)	18/79 (23%)	<0.001
Patch Grafts	0/3 (0%)	2/4 (50%)	-
Brisk Bleeding	16/39 (41%)	1/34 (3%)	<0.001
Oozing	48/97 (50%)	29/94 (26%)	<0.001

Adverse Events (through the 6 week post-discharge follow-up): Summary Information

	CoSeal	Control	p-value
Number of patients	74	74	
Number of patients w/AEs	56/74 (76%)	49/74 (66%)	0.255
Number of total AEs	188	147	
Mean AEs per patient	2.5	2.0	
Median AEs per patient	2.0	1.0	

All of the adverse events seen in the treatment group were rated by the investigators as “unlikely related” (7%) or “definitely not related” (93%) to the use of CoSeal. The following types of adverse events were seen: edema, fever, erythema, infection, thrombosis, occlusion, hematoma, etc. (A detailed list of the types and numbers of adverse events can be found in the Summary of Safety and Effectiveness Data, Part 2 of this panel package, page 2-004).

Adverse Events: Fevers

	CoSeal	Control
Number of patients	74	74
Total Fevers	13/74 (18%)	4/74 (5%)
Mild Fever	8/74 (11%)	3/74 (4%)
Moderate Fever	3/74 (4%)	0/74 (0%)
Severe Fever	2/74 (3%)	1/74 (1%)

This table is based on information submitted through 7/9/01. At the 7/20/01 100-Day teleconference with the sponsor, the sponsor indicated that they were undertaking a re-audit of all of the CoSeal and Control patient charts to determine if the incidences of elevated temperatures were accurately reported in the Case Report Forms for the clinical study. This new temperature information is included in Part 5.a.iv.1 (Analysis of Patient Temperature Data) of your panel package. Prior to the panel mailing, FDA did not have the opportunity to review this information.

European Multi-Center Clinical Study

A non-randomized study of 131 patients undergoing peripheral vascular surgery and treated with CoSeal in Europe indicated that sealing bleeding from ePTFE grafts is more difficult than sealing bleeding from Dacron or autologous tissue grafts.

Effectiveness Results: Hemostasis within 10 Minutes

	CoSeal (Intent to Treat)	CoSeal (Evaluable Sites)
Number of sites treated	219	202
Success by site (all indications)	193/219 (88%)	193/202 (96%)
Bypass Grafts	141/165 (85%)	141/149 (95%)
AV Grafts	34/36 (94%)	34/35 (97%)
Arteriotomy Sites	18/18 (100%)	18/18 (100%)
Patch Grafts		
Success by Material Type		
EPTFE Graft	97/119 (82%)	97/106 (92%)
Dacron Graft	35/37 (95%)	35/35 (100%)
Autologous Tissue	61/63 (97%)	61/61 (100%)

There were 92 adverse events in 57 of the 131 patients. Included in these adverse events, were 2 patients who developed fevers on the first post-operative day. Neither of these patients was treated for the fever, and neither patient had any other adverse event. Please see page 4 of Dr. Chandeysson's attached review (Tab A) for additional details regarding these and other adverse events.

European Feasibility Study

A non-randomized feasibility study of 15 patients undergoing peripheral PTFE grafting for arterial reconstruction and treated with CoSeal was conducted in Europe to investigate the safety of CoSeal use. There were 11 serious adverse events in 5 of the 15 patients. Three of the 15 study patients developed a fever (rated as a non-serious adverse event). Please see page 3 of Dr. Chandeysson's attached review (Tab A) for additional details.

FDA Identified Clinical Issues

As outlined in Dr. Chandeysson's attached 7/18/01 review (Tab A), his primary concern regarded:

- The higher number of fevers seen in the CoSeal group (US multi-center study), based on data submitted through 7/9/01. New data regarding pre-clinical pyrogenicity testing and re-audit of clinical study patient charts was not available for FDA review prior to mailing this panel package.

Panel Please Note:

There will be a panel question regarding implications of the findings regarding elevated temperature for the assessment of device safety, and the clinical importance of the overall adverse events and complications observed in these patients. (Please also see the discussion regarding pre-clinical pyrogenicity testing on page 4 of this memorandum.)

FDA Statistical Issues

As outlined in Dr. Zhou's attached 6/8/01, 7/6/01 and 7/10/01 reviews and emails (Tab B), her primary concerns regarded:

- Stratification of adverse events by study (US multi-center, OUS multi-center, & OUS feasibility) and by type of surgery (e.g., AV grafting, bypass grafting, etc.)
- number of adverse events in CoSeal group as compared to the control (US multi-center study)
- Demonstration of randomization by investigator and type of surgery (US multi-center study)
- Demonstration of poolability (US multi-center study)

Dr. Zhou had no questions regarding the demonstration of equivalence in the US multi-center study, and her questions regarding the issues identified above, have been addressed to her satisfaction.

Indications, Contraindications, Warnings, and Precautions (per proposed labeling)

CoSeal is indicated for use in sealing arterial and/or venous reconstructions

CONTRAINDICATIONS: none

WARNINGS:

- Do not inject CoSeal into vessels.
- CoSeal is intended for use as a sealant and is not to be used in place of sutures, staples or mechanical closure.

PRECAUTIONS:

- The safety and performance of CoSeal have not been established in children and pregnant women.
- Preclinical studies support the safe use of CoSeal at treatment volumes $\leq$ 3 ml/Kg body weight.

Note that FDA has asked the sponsor for clarifications regarding the last precaution on treatment volumes (8/3/01 100-Day Status Letter).

When the US multi-center study was designed, FDA recommended that patients requiring vascular reconstruction for peripheral indications, aneurysmectomy and aortic repair should not be included in the same study. FDA made this recommendation because the different indications present different placement, pressure and flow conditions that could impact on the sealant's ability to work as intended. **The current label and Summary of Safety and Effectiveness Data include very general indications and instructions for use, while the clinical study was designed to investigate only peripheral use.**

Panel Please Note:

There will two panel questions: one asking whether the studies provide adequate justification for the labeled indication, and the second requesting any other recommendations or comments regarding the labeling of this device.